Remarks

Applicant has amended independent claim 29 to include the phrase "a dissolution curve similarity fit factor *F2* of at least about 79" under 37 C.F.R. § 1.312, Amendment after Allowance, as recommended by the Examiner. This phrase is also the substance of dependent claims 31, 37 and 43. Thus, Applicant has canceled dependent claims 31, 37 and 43 without prejudice. Support for the amendment is found in the specification as filed pages 16-17 and in claim 1 as originally presented, copies of which are attached hereto. No new matter is added.

In Applicant's response of December 22, 2003, Applicant filed an amendment canceling all pending claims and submitting new claims as suggested by the Examiner in the Office Action of September 9, 2003. In the December 2003 amendment, Applicant inadvertently removed this phrase from an independent claim and moved it to dependent claims. The present amendment is needed because the phrase removed to currant claims 31, 37 and 47 is an element of the invention. This element provides a factor needed to properly analyze the results. After reviewing the application upon receiving the Notice of Allowance, the error was detected. The present amendment does not require further search or examination. The amended claims presented herewith are patentable as the only change is incorporating the phrase of independent claims 31, 37 and 47 to dependent claim 29. All of those claims were allowable in the Notice of Allowance mailed January 27, 2004.

Entrance of the present amendment is respectfully requested and early passage of the above-referenced application for U.S. patent to issuance is earnestly solicited. Applicant has included a clean copy of the pending claims in Appendix A. Should the Examiner have any questions or require additional information or clarification, Applicant requests that the Examiner contact the attorney of record at the number noted below.

Respectfully submitted,

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CERTIFICATION UNDER 37 C.F.R. §1.10

I hereby certify that the attached papers are being deposited with the United States Postal service as: "Express Mail Post Office to Addressee" Service under 37 C.F.R. §1.10 on 27 April 2004 and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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APPENDIX A

29. A method of treating cholesterol disorders with an intermediate release nicotinic acid formulation without causing treatment limiting hepatotoxicity, elevations in uric acid, or glucose levels such that use of said formulation is discontinued comprising;

orally administering once per day an effective amount of said formulation for treating said disorder, said formulation having a dissolution curve similarity fit factor *F2* of at least bout 79, and an *in vitro* dissolution profile, when measured in a type I dissolution apparatus (basket), according to U.S. Pharmacopiea XXII, in about 37°C in deionized water at about 100 rpm, as follows:

(a) less than about 15% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 15% and about 30% of the nicotinic acid is released after about 3 hours in the apparatus;

(c) between about 30% and about 45% of the nicotinic acid is released after about 6 hours in the apparatus;

(d) between about 40% and about 60% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 50% and about 75% of the nicotinic acid is released after about 12 hours in the apparatus; and

(f) at least about 75% of the nicotinic acid is released after about 20 hours in the apparatus.

30. The method of claim 1, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

31. (Cancelled)

32. The method of claim 29, wherein said formulation is a tablet.

33. The method of claim 32, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg and about 750mg.

34. The method of claim 29, wherein the once per day dose is administered during the evening or at night.

35. The method of 29, wherein the *in vitro* dissolution profile is as follows:

(a) between about 9.6% and about 13.8% of the nicotinic acid is released after about 1 hour in the apparatus;

(a) between about 21.2% and about 27.8% of the nicotinic acid is released after about 3 hours in the apparatus;

(b) between about 35.1% and about 44.2% of the nicotinic acid is released after about 6 hours in the apparatus;

(c) between about 45.6% and about 58.5% of the nicotinic acid is released after about 9 hours in the apparatus;

(d) between about 56.2% and about 72% of the nicotinic acid is released after about 12 hours in the apparatus; and

(e) at least about 75% of the nicotinic acid is released after about 20 hours in the apparatus.

36. The method of claim 35, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

37. (Cancelled)

38. The method of claim 35, wherein said formulation is a tablet.

39. The method of claim 38, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg, and about 750mg.

40. The method of claim 35, wherein the once per day dose is administered during the evening or at night.

(Remainder of page left intentionally blank.)

41. The method of claim 29, wherein the *in vitro* dissolution profile is as follows:

(a) between about 9.8% and about 12.3% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 20.9% and about 26.7% of the nicotinic acid is released after about 3 hours in the apparatus;

(c) between about 35.3% and about 44.1% of the nicotinic acid is released after about 6 hours in the apparatus;

(d) between about 44.8% and about 58.7% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 59.5% and about 70.7% of the nicotinic acid is released after about 12 hours in the apparatus; and

(f) at least about 75% of the nicotinic acid is released after about 20 hours in the apparatus.

42. The method of claim 41, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

43. (Cancelled)

44. The method of claim 41, wherein said formulation is a tablet.

45. The method of claim 44, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg, and about 750mg.

46. The method of claim 41, wherein the once per day dose is administered during the evening or at night.

(Remainder of page left intentionally blank.)

47. A method of treating cholesterol disorders with an intermediate release nicotinic acid formulation without causing treatment limiting hepatotoxicity, elevations in uric acid or glucose levels such that use of said formulation is discontinued, comprising;

orally administering once per day an effective amount of said formulation for treating said disorder, said formulation having a dissolution curve similarity fit factor *F2* of at least 44, and an *in vitro* dissolution profile, when measured in a type I dissolution apparatus (basket), according to U.S. Pharmacopiea XXII, in about 37°C in deionized water at about 100 rpm, as follows:

(a) less than about 15% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 15% and about 30% of the nicotinic acid is released after about 3 hours in the apparatus;

(c) between about 30% and about 45% of the nicotinic acid released after about 6 hours in the apparatus;

(d) between about 40% and about 60% of the nicotinic acid is released after about 9 hours in the apparatus;

(e) between about 50% and about 75% of the nicotinic acid released after about 12 hours in the apparatus; and

(f) at least about 75% of the nicotinic acid is released after about 20 hours in the apparatus.

48. The method of claim 47, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

49. The method of claim 47, wherein said formulation is a tablet.

50. The method of claim 49, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg, about 750mg and about 1000mg.

51. The method of claim 47, wherein the once per day dose is administered during the evening or at night.

52. The method of claim 47, wherein the *in vitro* dissolution profile is as follows:

(a) between about 9.6% and about 13.8% of the nicotinic acid is released after about 1 hour in the apparatus;

(b) between about 21.2% and about 27.8% of the nicotinic acid is released after about 3 hours in the apparatus,

(c) between about 35.1% and about 44.2% of the nicotinic acid is released after about 6 hours in the apparatus,

(d) between about 45.6% and about 58.5% of the nicotinic acid is released after about 9 hours in the apparatus,

(e) between about 56.2% and about 72% of the nicotinic acid is released after about 12 hours in the apparatus, and

(f) at least about 75% of the nicotinic acid is released after about 20 hours in the apparatus.

53. The method of claim 52, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

54. The method of claim 52, wherein said formulation is a tablet.

55. The method of claim 54, wherein said tablet contains nicotinic acid is an amount selected from the group consisting of about 375mg, about 500mg, and about 750mg.

56. The method of claim 52, wherein the once per day dose is administered during the evening or at night.

(Remainder of page left intentionally blank.)

57. The method of claim 47, wherein the *in vitro* dissolution profile is as follows:

(a) between about 9.8% and about 12.3% of the nicotinic acid is released after about 1 hour in the apparatus,

(b) between about 20.9% and about 26.7% of the nicotinic acid is released after about 3 hours in the apparatus,

(c) between about 35.3% and about 44.1% of the nicotinic acid is released after about 6 hours in the apparatus,

(d) between about 44.8% and about 58.7% of the nicotinic acid is released after about 9 hours in the apparatus,

(e) between about 59.5% and about 70.7% of the nicotinic acid is released after about 12 hours in the apparatus; and

(f) at least about 75% of the nicotinic acid is released after about 20 hours in the apparatus.

58. The method of claim 57, wherein approximately 100% of the nicotinic acid is released after about 20 hours in the apparatus.

59. The method of claim 57, wherein said formulation is a tablet.

60. The method of claim 59, wherein said tablet contains nicotinic acid in an amount selected from the group consisting of about 375mg, about 500mg, about 750mg and about 1000mg.

61. The method of claim 57, wherein the once per day dose is administered during the evening or at night.

Similarity between the test and the target dissolution curves within a tablet strength can be determined through the calculation of the fit factor F_2. See Moore JW, Flanner HH.: Mathematical comparison of dissolution profiles, Pharmaceutical Technology, 64-74 (June 1996), which is incorporated herein by reference in its entirety. In other words, the fit factor F_2 is calculated using the difference between the percent dissolved at each time point for each dissolution profile. If there is no difference between the percent dissolved at each time point, the fit factor F_2 equals 100. As the difference in percent dissolved increases, however, the fit factor F_2 value decreases. The fit factor F_2 is determined by the following equation:

$$F_2 = 50 \log \{[1 + 1/n \sum_{t=1}^{n} w_t (R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t is the dissolution value for the target profile at a time point t, T_t is the dissolution value for the test profile at the same time point t, n is the number of time points on the dissolution profile and w_t is an optional weight factor. This equation is a logarithmic transformation of the sum of the mean square error between the test and target profile, resulting in a number between 0 and 100. The fit factor F_2 is 100 when two dissolution profiles are identical and decreases as the two profiles become more dissilimar. In other words, the smaller the fit factor F_2, the farther apart the products are from one another. The fit factor F_2 will be positive as long as the average difference between the two curves is 100 or less.

The following Table 6 depicts the recommended fit factor F_2 values for each of the Niaspan® tablet strengths. The recommended values are based on the range of fit factors F_2 between lots used in the New Drug Application (NDA), made more specific by the determination of bioequivalence to a target lot of Niaspan® tablets.

Having described my invention, I claim:

(1) A method of treating a lipidemic disorder with a nicotinic acid formulation suitable for oral administration once-a-day as a single dose without causing drug-induced hepatotoxicity in an individual to a level and without causing drug-induced elevations in uric acid or glucose or both to levels which would require use of the nicotinic acid formulation to be discontinued by the individual, comprising:

orally administering to the individual once-a-day as a single dose an effective amount of an intermediate release nicotinic acid formulation without causing drug-induced hepatotoxicity in the individual to a level and without causing drug-induced elevations in uric acid or glucose or both to levels which would require use of the intermediate nicotonic acid formulation by the individual to be discontinued, the intermediate release nicotinic acid formulation having

a dissolution curve similarity fit factor F_2 of at least about 79, and

an *in vitro* dissolution profile, when measured in a type I dissolution apparatus (basket), according to U.S. Pharmacopeia XXII, at about 37°C in deionized water at about 100 rpm, as follows

(a) less than about 15% of the nicotinic acid is released after about 1 hour in the apparatus,

(b) between about 15% and about 30% of the nicotinic acid is released after about 3 hours in the apparatus,

(c) between about 30% and about 45% of the nicotinic acid is released after about 6 hours in the apparatus,

(d) between about 40% and about 60% of the nicotinic acid is released after about 9 hours in the apparatus,

(e) between about 50% and about 75% of the nicotinic acid is released after about 12 hours in the apparatus, and

(f) at least about 75% is released after about 20 hours in the apparatus.

TABLE 6

Criteria derived from:	250 and 325 mg tablet strengths	500mg tablet strength	750mg tablet strength	1000mg tablet strength
Bioequivalence Studies	≥79.0	≥79.0	≥79.0	≥44.0

The term "bioequivalence," as used herein, means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See Code of Federal Regulations, Title 21, April 1, 1997 edition, Part 320.1, Definitions *(e) Bioequivalence*, page 195, which is incorporated by reference herein in its entirety.

Table 7 also depicts the fit factor F_2 for thirteen (13) of the sixteen (16) over-the-counter SR niacin products referenced in Tables 5A and 5B compared to the dissolution curve of Niaspan®. As can be seen from the fit factor F_2 data in Table 7, the thirteen (13) over-the-counter SR niacin products are not bioequivalent to Niaspan®, in view of the fact that the fit factor F_2 is less than 79 for all such products.

TABLE 7

Brand	Niaspan® K4061A-1 500mg	GTRN 250 86A6014C 250mg	Nicobid MN0928 500mg	Goldline 12 12L51229 500mg	Goldline 87 87L51081 500mg	Goldline 89 89G5612C 500mg	Rugby M0 M070E 500mg	Rugby 5L 5L01707 500mg	Time Cap A051G 500mg	Major 5F00753 500mg	Upsher-Smith 16020 500mg	Geneva 4B124 500mg	Mason 501199 500mg	Endurance 11504 500mg		
F2	79	54.3	39.4	60.6		64.5	45.0	38.7	57.3	53.9	48.7	56.3	39.3	60.8	59.6	